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Case report

Intravenous veterinary ivermectin in a COVID-19 patient causing neurotoxicity

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ABSTRACT

Ivermectin administration for Coronavirus disease 2019 (COVID-19) infection has gained a lot of attention recently. Although ivermectin has a relatively good safety profile, serious adverse events may occur in patients given doses that are presumed experimental. Ivermectin for human use is available only as an oral formulation. Parenteral administration, as a subcutaneous injection, is possible in veterinary medicine only. In this brief report we describe an unprecedented case of a patient with severe neurotoxicity after intravenous administration of veterinary ivermectin for confirmed COVID-19 infection. The patient required hospitalization in the intensive care unit (ICU). The toxic serum concentration of ivermectin was determined by liquid chromatography/mass spectrometry - time of flight (LC/MS-TOF) with the value of 187.74 ng/mL.

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Introduction

Ivermectin is a broad-spectrum antiparasitic agent belonging to the class of avermectins (a class of macrocyclic lactones). To date, the U.S. Food and Drug Authority (FDA) has approved the use of ivermectin against head lice, lymphatic filariasis, onchocerciasis, strongyloidiasis, rosacea, and scabies [1]. Ivermectin is also included in the World Health Organization (WHO) list of essential medicines and is commonly used worldwide [2]. It acts by binding to the glutamate-dependent chloride channels of invertebrate nerve and muscle cells, causing an increase in membrane permeability, leading to neuromuscular paralysis and death of certain parasites. During the last two years there were attempts to repurpose the old drug for COVID-19 prevention and treatment. Ivermectin has been shown to inhibit the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cell cultures [3]. From the pharmacokinetic and pharmacodynamic point of view, however, it seems that achieving the plasma concentrations necessary for the antiviral efficacy would require administration of doses up to 100-fold higher than those approved for use in humans [4]. Because ivermectin is

used primarily in veterinary medicine, many people in Slovakia were trying to get veterinary products in the early phase of uncertainty about targeted anti COVID-19 treatment. However, FDA issued a warning in April 2020 that ivermectin intended for use in animals should not be used to treat COVID-19 in humans [5].

To date, according to the National Institute of Health (NIH) there is no convincing evidence-based data supporting the benefit of ivermectin use in the treatment of COVID-19 infection. Also, what needs to be considered is that there may be serious neurological adverse events during ivermectin treatment in those who are given higher than recommended doses. Ivermectin does not easily cross the blood-brain barrier since it is excluded by a P-glycoprotein drug pump. Therefore, the potential to cause neurotoxicity is mostly seen in cases of overdose [6].

We would like to present the first case report in the literature of intravenous administration of veterinary ivermectin in a patient treated for COVID-19 infection, which resulted in severe neurotoxicity requiring hospitalization in the ICU at the Louis Pasteur University Hospital (LPUH), Kosice, Slovakia.

Case report

A 50-year-old woman with no history of serious illness was evaluated at The Department of Infectology and Travel Medicine because of fever, malaise, dyspnea, and altered mental status, scoring 3 points on Glasgow coma scale (GCS). Her symptoms started 5 days before, altered mental status was present on the day

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of evaluation in the hospital. Real-time polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 positivity on the day the symptoms started.

All relevant history information was taken from her accompanying husband. Three days before, she was started on ivermectin treatment (5 tablets of 3 mg ivermectin every 8 h, i.e., 45 mg/day) by her general practitioner (GP). On the day before hospital evaluation (1.00 p.m.), she had been given an infusion of intravenous ivermectin (veterinary ivermectin formulations approved only for subcutaneous use in animals in Slovakia) by her GP. The patient had been given 20 mg/2 mL of veterinary ivermectin (supplied as a 20 mL vial containing ivermectin with a concentration of 10 mg/1 mL), which would be appropriate for 100 kg animal (suggested ivermectin dosing of 0.2 mg/kg). After the infusion she vomited several times, was fatigued, and there was involuntary incontinence of urine.

During the evaluation at our department (3.00 p.m.) her vital signs were as follows: blood pressure 90/60 mm Hg, pulse was 102 and regular, oxygen saturation 85% on room air, temperature was 39 °C, and respiratory rate 23. Further physical examination revealed crackles in both lungs. Heart, abdomen, and legs were normal. Her weight was 100 kg.

On neurologic examination she was almost unresponsive, verbal contact was with latency, there was quadriparesis with myoclonic jerks of upper and lower limbs, signs of extrapyramidal syndrome, ptalism, both pupils were mydriatic, and no signs of nuchal rigidity were present. No cranial nerve abnormalities could be found. Further physical examination revealed no other pathological signs.

A computed tomographic (CT) scan and angiography of the brain revealed no pathology. High-resolution CT scan of the lungs showed bilateral peripheral patchy opacities, consolidation and thickening of peri lobular interstitium typical for COVID-19 pneumonia, and a small right pleural effusion. Semiquantitative evaluation showed a severity score of 12/25. No pneumothorax was observed (Fig. 1).

The patient was admitted to the Neurology Department with the diagnosis of COVID-19 pneumonia and presumed ivermectin overdose neurotoxicity. Laboratory testing revealed an elevation of aminotransferases, gamma glutamyl transpeptidase, C-reactive protein, lactate dehydrogenase, and low levels of albumin. Hemoglobin, platelet count, and white blood cells were normal. Tests for coagulation showed D-dimer level of 1.39 mg/L (reference range, <0.5) and fibrinogen of 6.54 g/L (reference range, 1.8–3.5). Other coagulation parameters were normal. All laboratory results are summarized in Table 1. Blood specimen was obtained for toxicology evaluation (the same day as the admission to the hospital 6.00 p.m.). The specimen was frozen to –80 °C as required for proper sample storage and handling.

Table 1
Laboratory data.

Variable	Reference range, Adults	On admission	On discharge
Hematocrit (%)	36–46	0,39	0,37
Hemoglobin (g/dL)	12–16	12,52	11,85
White-cell count ($\times 10^9/L$)	4,0–10	5,21	12,04
Differential count ($\times 10^9/L$)			
Neutrophils	1,4–6,5	4,43	6,84
Lymphocytes	1,5–4,0	0,49	3,85
Monocytes	0,25–0,6	0,28	1,27
Eosinophils	0,05–0,25	0	0,04
Platelet count ($\times 10^9/L$)	150–400	240	523
Prothrombin-time international normalized ratio	0,85–1,15	1,06	0,95
D-dimer (mg/L)	< 0,5	1,39	1,48
Fibrinogen (g/L)	1,8–3,5	6,54	3,17
Lactate dehydrogenase ($\mu\text{kat/L}$)	2,25–4,12	10,1	4,15
C-reactive protein (mg/L)	< 5	47,3	1,09
Urea (mmol/L)	2,8–7,2	2,95	3,62
Creatinine (mmol/L)	49–90	51,4	64
Albumin (g/L)	35–52	25,8	34,8
Bilirubin ($\mu\text{mol/L}$)	5–21	22,6	11,3
Aspartate aminotransferase ($\mu\text{kat/L}$)	0,05–0,6	2,51	0,55
Alanine aminotransferase ($\mu\text{kat/L}$)	0,05–0,6	1,68	1,3
Gamma glutamyl transpeptidase ($\mu\text{kat/L}$)	0,05–0,63	5,41	2,6
Alkaline phosphatase ($\mu\text{kat/L}$)	0,5–2	2,18	1,78
Procalcitonin ($\mu\text{g/L}$)	< 0,5	0096	0057
Lactate (mmol/L)	0,5–2,2	1,53	2,1
Interleukin 6 (ng/L)	1,5–7	19,3	3,19
Troponin ($\mu\text{g/L}$)	0003–0014	0022	–
CD4+ ($\times 10^9/L$)	0,3–1,4	0,46	–
CD8+ ($\times 10^9/L$)	0,2–0,9	0,19	–
CD19+ ($\times 10^9/L$)	0,1–0,5	0,28	–
Natural killer cells	0,09–0,6	0,20	–
Streptococcal antigen (urine)	< 1	0,23	–
Legionella antigen (urine)	< 1	0,08	–
<i>Chlamydia pneumoniae</i> IgM and IgG	negative	negative	–
<i>Mycoplasma pneumoniae</i> IgM and IgG	negative	negative	–
SARS-CoV-2 RT-PCR	negative	positive	–
Urine culture	negative	negative	–
Sputum culture	negative	negative	–

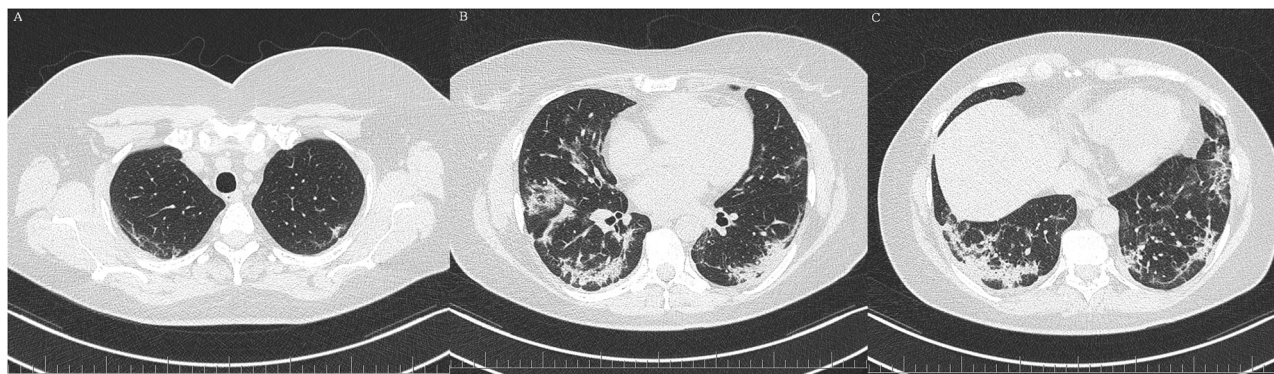


Fig. 1. High resolution CT scan of the lungs Panel A: upper lungs show septal thickening. Panel B, C: mid-lungs, lower lungs with peripheral ground-glass and consolidative opacities. Severity score 12/25.

Treatment with dexamethasone, N-acetylcysteine, low molecular weight heparin (prevention dose), bisulepin (an antihistamine), silymarin (milk thistle extract), vitamin D, vitamin C, polyoxidonium (an immune enhancer), and intravenous fluids was started. Patient was receiving supplemental oxygen through the nasal cannula at a rate of five liters per minute. This case was also consulted with the Slovak National Toxicology Center. No specific antidote for assumed ivermectin overdose was recommended, only symptomatic and supportive care. After 24-hour hospitalization at the Neurology Department, the patient was transferred to the intensive care unit at the Department of Internal Medicine for further monitoring (GCS 9–8). During the next few days, she had dysgeusia and vertigo, but became responsive and was able to walk short distances. COVID-19 symptoms did not worsen, she had a cough and required only low volumes of oxygen. During hospitalization follow-up neurological assessment was performed. There was an improvement in mental status, the patient was awake, with normal cognitive functions, and no focal deficit was observed. The patient had leg weakness, slightly improving until discharge.

The result from the toxicology laboratory (Health Care Surveillance Authority) returned positive. The concentration of ivermectin was assessed by LC/MS-TOF. The concentration of ivermectin was 187.74 ng/mL, and there were two metabolites detected (ivermectin M1, ivermectin M3). Screening also revealed low concentrations of hydrocortisone, cetirizine, and ofloxacin.

After 10-day hospitalization the patient was discharged to home quarantine with slight overall weakness. She was normoxic and was able to take care of herself.

Discussion

The discovery of ivermectin's activity against SARS-CoV-2 gave us a reason for optimism, but off-label and compassionate use may have profound consequences and may result in unfavorable adverse events [7]. Many doctors, despite up-to-date research and/or unavailability of effective outpatient treatment regimens for COVID-19, try to push the boundary of evidence-based medicine and tend to put their hope into the old, repurposed drugs that have the laboratory potential to suppress the virus, but do not provide significant results in adequate clinical trials.

The patient in our case report was a female, although neurotoxicity in the form of encephalopathy after ivermectin use was described mainly in males, probably due to the protective effect of female hormones [8].

She was administered 45 mg/day of oral ivermectin during a three-day period and 20 mg of intravenous veterinary ivermectin formulation (155 mg overall in 4 days). According to literature, ivermectin is available for human use only as an oral formulation (either a 3-mg tablet or 6-mg scored tablet) and is administered as a single dose of 0.2 mg/kg for parasitic infection, however, several other dosing options were proposed for COVID-19 patients (e.g. 0.2–0.6 mg/kg/day for 3–5 days) [9,10]. As noted in former studies, the activity of ivermectin in cell culture has not been reproduced in mouse infection models against many of the viruses (Zika virus, Yellow fever virus, Dengue virus, West Nile virus, Chikungunya virus and others) and has not been clinically proven either, in spite of ivermectin being available globally [11]. This is likely related to the pharmacokinetics and therapeutic safety window for ivermectin. The blood levels of ivermectin at safe therapeutic doses are in the 20–80 ng/mL range, while the activity against SARS-CoV2 in cell culture is in the microgram range [12]. Another study found that the serum C_{max} of ivermectin is proportional to dose, with a value of 38–46 ng/mL reached after an oral therapeutic 0.2 mg/kg dose [13]. The ivermectin dose administered to our patient, even according to aforementioned protocols, is high. Moreover, the intravenous administration of veterinary ivermectin in our patient is unprecedented. Our patient had a serum concentration

of ivermectin almost five times higher than considered normal. This is most likely attributed to a combination of high oral dosage and intravenous administration of veterinary ivermectin. Because safety and pharmacokinetic data in human studies are scarce, our case report brings new insight into tolerability of higher than recommended doses of ivermectin. Our findings show that dosage of oral ivermectin of more than 0.4 mg/kg/day, plus intravenous bolus of veterinary product leads to neurotoxicity. For sure, a major part in this adverse event plays intravenous administration. Therefore, intravenous administration of any ivermectin formulations should be strongly discouraged, even at doses extrapolated from oral ivermectin use. We have used the standard diagnostic methodology (LC/MS-TOF) since this method is robust and suitable for clinical pharmacokinetic studies [14].

It is also clear that neurotoxicity after intravenous ivermectin administration develops very rapidly, despite the presence of P-glycoprotein drug pump that limits the action of ivermectin in the central nervous system. Recent findings suggest that the severe central nervous system side effects seen in various vertebrates may be due to an absence of, or functional deficiency in P-glycoprotein [15]. However, we were not able to assess this possibility in our patient. It has been also postulated, that fluoroquinolones inhibit P-glycoprotein efflux pump and therefore may be responsible for increased ivermectin penetration to tissues. Other potential explanations include concomitantly administered drugs which inhibit CYP3A4 (e.g., corticosteroids) and drugs that have a CNS-effect (antihistamines). Since the LC/MS-TOF detected low concentration of ofloxacin, hydrocortisone, and cetirizine in the serum sample, we cannot exclude the synergistic effect of co-administered drugs on neurotoxicity either [16].

Most of the safety and pharmacokinetic data on oral administered ivermectin are from doses of 0.15–0.20 mg/kg. In an animal study by Rafael et al. doses of ivermectin in the range of 0.22–0.86 mg/kg were not harmful to intestinal tissue and blood cells in general [17].

Another study by Njoo et al. did not show a correlation of ivermectin serum concentration and severity of neurotoxicity, but it is necessary to point out that all patients in this study had ivermectin concentration in the reference range [18]. However, according to our observation, high doses of ivermectin resulting in high serum concentrations (higher than the reference range), may be harmful to the brain tissue and can negatively contribute to the liver damage and lymphopenia already present in COVID-19 patients. Thus, concentration dependent neurotoxicity seems to be pronounced in patients exceeding the reference range of ivermectin serum concentration.

Another important finding is that once the drug is withdrawn, there is slow, but almost complete resolution of neurotoxicity. The slow nature of symptoms resolution may be explained by ivermectin's ability to persist in the brain tissue for prolonged periods of time, as documented in one case series with orally and subcutaneously administered ivermectin for *Strongyloides* infection [19]. Also, the elimination half-life of the metabolites of ivermectin is longer than that of the parent drug, at about 3 days [18].

The intravenous administration of the drug in our case, did not result in a fatal outcome. However, case reports of fatal encephalopathy during ivermectin treatment for onchocerciasis were described. The drug probably induces a paralysis of the microfilariae with inflammatory reaction (Mazzotti reaction). If the microfilarial density is high, the process of microfilarial paralysis and subsequent passive drainage to blood circulation can lead to an embolization in the brain capillaries and to a fatal encephalopathy [20]. The different mechanism of neurotoxicity may explain the non-fatal outcome in our patient.

Conclusion

The unique nature of this case report is that there are no published data on intravenous administration of ivermectin in humans

in the literature whatsoever. This rare occasion gave us the opportunity to draw several conclusions. We have observed rapid deterioration of neurological status after single intravenous infusion of ivermectin (minutes). Intravenous administration was responsible mainly for neurotoxicity; moderate elevation of liver enzymes and lymphopenia may have been caused by combination of COVID-19 disease and ivermectin use. The neurotoxicity was severe and required hospitalization in the ICU. The predominant signs of neurotoxicity were altered mental status, quadriparesis, myoclonic jerks of upper and lower limbs, signs of extrapyramidal syndrome, ptialism, and mydriasis.

Although ivermectin has an excellent safety profile, we must be vigilant about serious adverse events that may result from an off-label use in COVID-19 infection. According to our observation, physicians experimenting with any kind of ivermectin treatment should avoid an intravenous administration of this drug due to the substantial risk of acute onset of severe neurotoxicity. Symptomatic and supportive treatment for ivermectin overdose is the only therapeutic strategy. It is noteworthy that even after intravenous administration of ivermectin, there was no permanent neurological damage, and the resolution of symptoms was slow but complete. In a patient with COVID-19 infection and altered mental status, neurotoxicity caused by ivermectin treatment should be added to our list of differential diagnoses.

CRedit authorship contribution statement

Stefan Porubcin: Writing – original draft. **Alena Rovnakova:** Data curation. **Ondrej Zahornacky:** Supervision. **Pavol Jarcuska:** Writing – review & editing.

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Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Conflict of interest

None to declare for all authors.

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